Liver Cancer

Research Article

Liver Cancer
DOI: 10.1159/000527175

Received: May 24, 2022
Accepted: September 11, 2022
Published online: October 4, 2022

Tislelizumab in Patients with Previously Treated Advanced Hepatocellular Carcinoma (RATIONALE-208): A Multicenter, Non-Randomized, Open-Label, Phase 2 Trial

Zhenggang Ren[a] Michel Ducreux[b] Ghassan K. Abou-Alfa[c] Philippe Merle[d] Weijia Fang[e] Julien Edeline[f] Zhiwei Li[g] Lihua Wu[g] Eric Assenat[h] Sheng Hu[i] Lorenza Rimassa[j] Tao Zhang[k] Jean-Frédéric Blanc[l] Hongming Pan[m] Paul Ross[n] Chia-Jui Yen[o] Albert Tran[p] Guoliang Shao[q] Mohamed Bouattour[r] Yajin Chen[s] Tim Meyer[t] Jinlin Hou[u] David Tougeron[v] Yuxian Bai[w] Ming-Mo Hou[x] Zhiqiang Meng[y] John Wu[z] Vincent Li[A] Sandra Chica-Duque[B] Ann-Lii Cheng[C]

[a]Department of Hepatic Oncology, Liver Cancer Institute, Zhongshan Hospital, Fudan University, and Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, Shanghai, China; [b]Medical Oncology Department, Gustave Roussy, INSERM U1279, Paris-Saclay University, Villejuif, France; [c]Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Medical College at Cornell University, New York, NY, USA; [d]Department of Hepatology, Hospital La Croix-Rousse, Lyon, France; [e]Department of Medical Oncology, The First Affiliated Hospital Zhejiang University, Hangzhou, China; [f]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France, and ARPEGO (Accès à La Recherche Précoce Dans Le Grand-Ouest) Network, Rennes, France; [g]Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University, Hangzhou, China; [h]Department of Oncology, CHRU Saint Eloi, Montpellier, France; [i]Department of Internal Medicine-Oncology, Hubei Cancer Hospital, Wuhan, China; [j]Medical Oncology and Hematology Unit, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (Milan), Italy, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [k]Abdominal Oncology Department, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [l]Service Hépato-Gastroentérologie et Oncologie Digestive, Groupe Hospitalier Sud - Hôpital Haut Lévêque, Bordeaux, France; [m]Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China; [n]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust and Department of Oncology, King's College Hospital NHS Foundation Trust, London, UK; [o]Division of Hematology and Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; [p]Département Digestif, Université Côte d'Azur, Nice, France, and Centre Hospitalier Universitaire de Nice, Nice, France, and Centre Méditerranéen de Médecine Moléculaire, INSERUM U1065, Université Côte d'Azur, Nice, France; [q]Department of Radiology, Zhejiang Cancer Hospital, Hangzhou, China; [r]Department of Digestive Oncology, APHP Hôpitaux Universitaires Paris Nord Val de Seine, Hôpital Beaujon, Clichy, France; [s]Department of Hepatobiliary Surgery, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; [t]Academic Department of Oncology, Royal Free Hospital NHS Trust, Pond Street, London, UK; [u]State Key Laboratory of Organ Failure Research, Guangdong Key Laboratory of Viral Hepatitis Research, Nanfang Hospital, Southern Medical University, Guangzhou, China; [v]Gastroenterology and Hepatology Department, University of Poitiers and Department of Gastroenterology and Hepatology, Poitiers University Hospital, Poitiers, France; [w]Department of Gastrointestinal Oncology, Harbin Medical University Cancer Hospital, Harbin, China; [x]Department of Oncology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan; [y]Department of Integrative Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [z]Biostatistics, BeiGene USA, Inc., Ridgefield Park, NJ, USA; [A]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [B]Clinical Development, BeiGene USA, Inc., San Mateo, CA, USA; [C]Department of Oncology, National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan

Zhenggang Ren, Michel Ducreux, and Ghassan K. Abou-Alfa are co-first authors. Lihua Wu: affiliation at time of the study.
A full list of investigators is provided in online supplementary Table S1 at www.karger.com/doi/10.1159/000527175.

Karger@karger.com
www.karger.com/lic

Correspondence to:
Ghassan K. Abou-Alfa, abou-alg@mskcc.org

Keywords
Tislelizumab · Hepatocellular carcinoma · Immunotherapy · Pretreated patient population

Abstract
Introduction: Tislelizumab (anti-programmed cell death protein 1 antibody) showed preliminary antitumor activity and tolerability in patients with advanced solid tumors, including hepatocellular carcinoma (HCC). This study aimed to assess the efficacy and safety of tislelizumab in patients with previously treated advanced HCC. ***Methods:*** The multiregional phase 2 study RATIONALE-208 examined single-agent tislelizumab (200 mg intravenously every 3 weeks) in patients with advanced HCC with Child-Pugh A, Barcelona Clinic Liver Cancer stage B or C, and who had received one or more prior lines of systemic therapy. The primary endpoint was objective response rate (ORR), radiologically confirmed per Response Evaluation Criteria in Solid Tumors version 1.1 by the Independent Review Committee. Safety was assessed in patients who received ≥1 dose of tislelizumab. ***Results:*** Between April 9, 2018, and February 27, 2019, 249 eligible patients were enrolled and treated. After a median study follow-up of 12.7 months, ORR was 13% (n = 32/249; 95% confidence interval [CI], 9–18), including five complete and 27 partial responses. The number of prior lines of therapy did not impact ORR (one prior line, 13% [95% CI, 8–20]; two or more prior lines, 13% [95% CI, 7–20]). Median duration of response was not reached. The disease control rate was 53%, and median overall survival was 13.2 months. Of the 249 total patients, grade ≥3 treatment-related adverse events were reported in 38 (15%) patients; the most common was liver transaminase elevations in 10 (4%) patients. Treatment-related adverse events led to treatment discontinuation in 13 (5%) patients or dose delay in 46 (19%) patients. No deaths were attributed to the treatment per investigator assessment. ***Conclusion:*** Tislelizumab demonstrated durable objective responses, regardless of the number of prior lines of therapy, and acceptable tolerability in patients with previously treated advanced HCC.

Introduction

The incidence of hepatocellular carcinoma (HCC) is increasing, and the prognosis remains poor [1, 2], with a 1-year overall survival (OS) rate of approximately 15–25% [3, 4]. Globally, recommended second-line targeted treatments after atezolizumab plus bevacizumab, sorafenib, or lenvatinib for advanced HCC include the multi-kinase inhibitors regorafenib [5, 6] and cabozantinib (second- or third-line) and the vascular endothelial growth factor receptor 2 inhibitor ramucirumab (for patients with α-fetoprotein [AFP] ≥400 ng/mL) [5, 7, 8]. In recent years, immuno-oncology therapies that target the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway [9, 10] have been approved as recommended second-line therapies for patients with advanced HCC based on phase 2 studies [7, 8, 11, 12]. Nivolumab plus ipilimumab and pembrolizumab as a single agent received accelerated approval in the USA [12]; and camrelizumab as a single agent received approval in China [7, 8, 11]. However, a confirmatory pembrolizumab study (KEYNOTE-240) did not confirm an improvement in OS [13]. Despite this, continued approval of pembrolizumab was recommended by the Food and Drug Administration's Oncologic Drugs Advisory Committee [13]. More recently, a phase 3 pembrolizumab study (KEYNOTE-394) in patients with previously treated advanced HCC met its primary endpoint of OS [14].

Although these recommended treatments have improved survival, the survival benefits are modest. Furthermore, the multi-kinase inhibitors have suboptimal tolerability [15]. For patients with HCC, an unmet need for a more durable and tolerable therapy than existing options beyond the first-line setting remains, especially for those who are not candidates to receive tyrosine kinase inhibitors or antiangiogenic treatments [8]. At the time this study was initiated (November 2017), sorafenib was the only treatment available in the first-line setting and no second-line treatment had been approved [8]. To date, only cabozantinib is recommended in the third-line setting in certain regions [8, 16–18], underscoring the need for additional novel therapies that can provide greater efficacy and a more tolerable safety profile beyond the second-line setting [7, 8].

Tislelizumab, a monoclonal antibody with high affinity and binding specificity for PD-1, was designed to minimize binding to Fc gamma receptors on macrophages to limit antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy (online suppl. Fig. S1; see www.karger.com/doi/10.1159/000527175 for all online suppl. material) [19]. Tislelizumab has shown antitumor activity and a tolerable safety profile consistent with other PD-1/PD-L1 inhibitors in several cancers, including non-small-cell lung cancer [20], urothelial carcinoma [21], esophageal squamous cell carcinoma [22], nasopharyngeal cancer [23], metastatic microsatellite instability-high/mismatch repair-deficient solid tumors [24],

and classical Hodgkin's lymphoma [25]. Two early-phase studies (NCT02407990 and CTR20160872) demonstrated single-agent tislelizumab (200 mg) administered intravenously (i.v.) every 3 weeks was generally well tolerated and showed preliminary antitumor activity in patients with advanced solid tumors, including HCC [26, 27]. This phase 2 study was designed to evaluate the efficacy and safety of single-agent tislelizumab as treatment for advanced HCC following ≥1 prior systemic treatment.

Methods

Study Design and Participants

This non-randomized, multicenter, open-label phase 2 study was conducted in 65 sites across eight countries in Europe and Asia. All relevant Institutional Review Boards/Independent Ethics Committees reviewed the protocol and amendments and approved the study, which was carried out in accordance with the International Conference on Harmonization Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations. The full protocol is available in the online supplementary materials. All patients provided written informed consent before participation.

Eligible patients were aged ≥18 years with histologically confirmed advanced HCC who had progressed on – or were intolerant to – ≥1 line of systemic therapy, such as sorafenib, chemotherapy, or any experimental therapy that had demonstrated efficacy in a phase 3 study. Inclusion criteria included a Barcelona Clinic Liver Cancer (BCLC) stage B or C disease not amenable to curative or locoregional therapy. Further inclusion criteria included Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, Child-Pugh A, ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and adequate organ function. Patients with hepatitis B virus (HBV) infection were required to have HBV DNA <500 IU/mL (or 2,500 copies/mL) and should have been receiving antiviral treatment per treatment guidelines. Exclusion criteria included prior therapy targeting immune checkpoints, evidence of metastases to the central nervous system, a history of grade ≥2 hepatic encephalopathy, clinically significant ascites, and main portal vein or inferior vena cava tumor thrombosis. Full eligibility criteria are provided in the online supplementary Methods.

Procedures

Patients received tislelizumab 200 mg i.v. every 3 weeks, on day 1 of each 21-day cycle, until intolerable toxicity, withdrawal of informed consent, or until the patient was no longer benefitting from study therapy in the investigator's opinion, whichever occurred first. Tumor assessments were performed by the Independent Review Committee (IRC) and investigator based on RECIST v1.1 every 6 weeks in the first 18 weeks and every 9 weeks thereafter until disease progression, withdrawal of consent, death, or start of a new anticancer therapy. Tumor imaging was performed by contrast-enhanced computed tomography or magnetic resonance imaging, including triphasic imaging of the liver. Patients with radiographic disease progression could continue tislelizumab treatment if protocol-specified criteria for progressive disease (PD) were met per investigator assessment and clinical benefit was evident.

Safety and tolerability were assessed throughout the study, including assessment of adverse events (AEs) and serious AEs, physical examination, vital signs, electrocardiogram, and laboratory tests. AEs were assessed and graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. All AEs were evaluated by the investigator for seriousness and causal relationship to study treatment from the start of treatment until either 30 days after the last dose of study treatment or initiation of new anticancer therapy, whichever occurred first. Full procedure details are provided in the online supplementary methods. PD-L1 expression was centrally assessed retrospectively by immunohistochemistry using the VENTANA PD-L1 (SP263) assay on newly obtained or archival pre-treatment tumor samples. Positive PD-L1 expression status was defined as PD-L1 staining in ≥1% of tumor cells.

Outcomes

The primary endpoint was objective response rate (ORR; defined as the proportion of patients achieving a complete response [CR] or partial response [PR]) by the IRC per RECIST v1.1 [28]. Secondary endpoints included assessment of the following by the IRC: duration of response (DoR; defined as the time between the first record of a confirmed response [CR/PR] and disease progression or death from any cause, in confirmed responders), progression-free survival (PFS), disease control rate (DCR; defined as patients with a CR, PR, or stable disease [SD]), and clinical benefit rate (CBR; defined as patients with a CR, PR, or durable SD, defined as SD for ≥24 weeks). Investigator-assessed secondary endpoints included ORR, DoR, PFS, DCR, and CBR. OS, the safety/tolerability profile of tislelizumab, and health-related quality of life were also secondary endpoints.

Statistical Analyses

The primary population for the efficacy and safety analyses was the safety population, which included all patients who received ≥1 dose of tislelizumab. Descriptive statistics were used to summarize the data. The null hypothesis of ORR = 7% (based on historical data) [29] was to be rejected if a binomial exact test obtained a one-sided p value ≤0.025. A sample size of 228 patients was calculated to provide a power of 0.97 for the primary efficacy analysis of ORR in the safety population. Of the total sample size, ≥100 of the enrolled patients were to have received 1 line of prior systemic therapy and ≥100 were to have received ≥2 lines of prior systemic therapy. Two-sided confidence intervals (CIs) of ORR were calculated using a binomial exact method. Patients without post-baseline tumor assessment were considered nonresponders. The subgroup analysis of ORR included prespecified analyses by treatment line, region, age-group, gender, ECOG PS, macrovascular invasion and/or extrahepatic spread, PD-L1 expression, baseline AFP (≤400 μg/L vs. >400 μg/L), BCLC staging (B vs. C), prior systemic therapy, local regional therapy, history of alcohol abuse, HCC etiology, and nonalcoholic steatohepatitis (NASH).

The Kaplan-Meier method was used to estimate time-to-event variables and corresponding quantiles in the responders. Two-sided CIs of DoR, PFS, and OS were calculated using the Brookmeyer and Crowley method. Two-sided CIs of DCR and CBR were calculated using a binomial exact method. Follow-up duration was calculated by the reverse Kaplan-Meier method. Patients who were lost to follow-up were censored at the last date they were known to

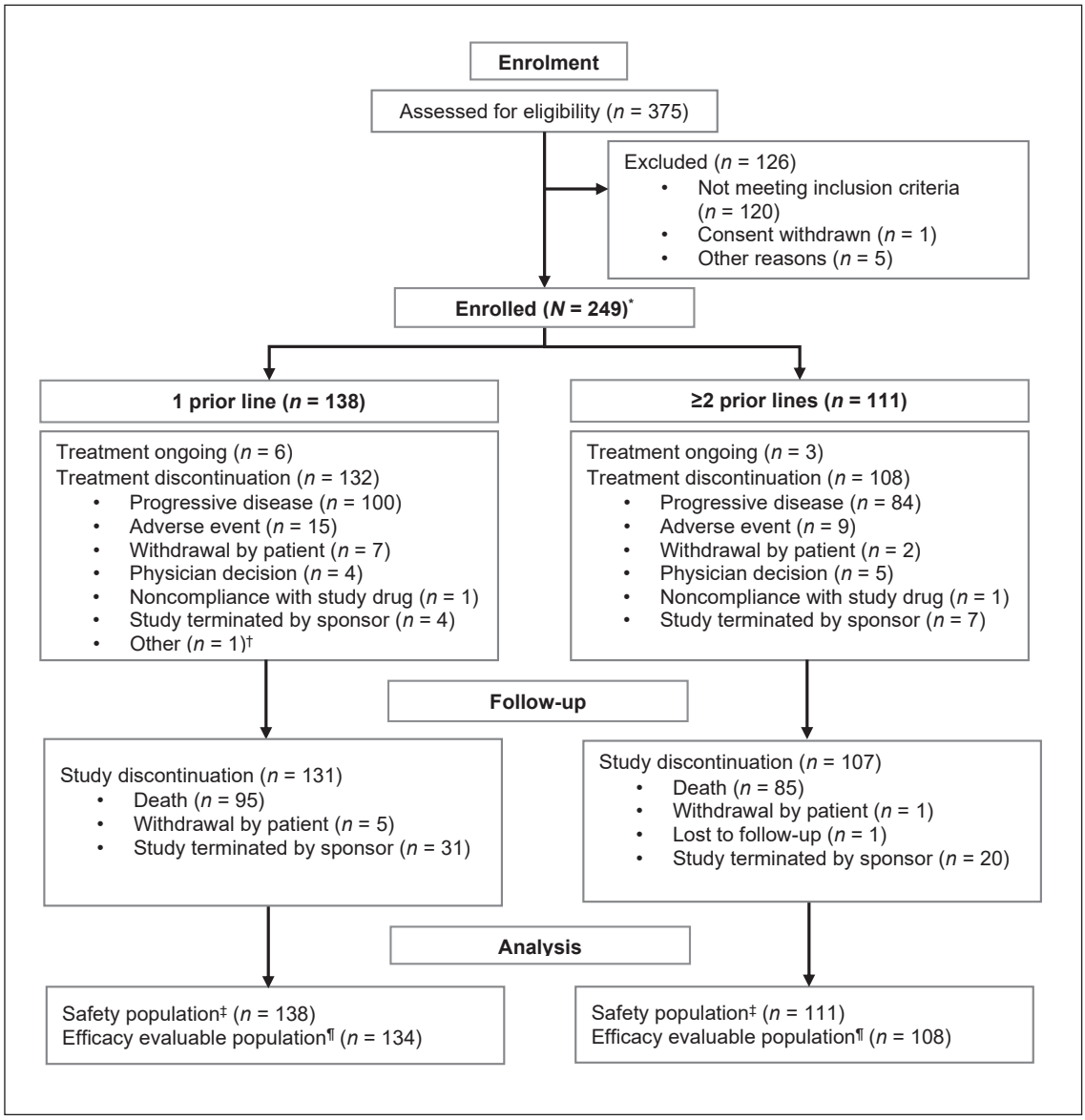


Fig. 1. Patient flow diagram. The data cutoff date is June 30, 2021. IRC, Independent Review Committee; ORR, objective response rate; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumorss. *Patients who were enrolled and treated with at least one dose of tislelizumab 200 mg Q3W. Major protocol deviations included 1 patient who received sorafenib as adjuvant therapy and 1 patient who received apatinib as first-line and sorafenib as second-line therapy. †The patient received other antitumor treatment in an external hospital. "Study terminated by sponsor" refers to study closure at the data cutoff. Patients who benefitted from tislelizumab treatment at the time of study termination were given a chance to continue the treatment in another treatment supply trial or program sponsored by BeiGene. ‡The safety population included all patients who received one or more doses of tislelizumab and was the primary population for efficacy and safety analyses. ¶The efficacy evaluable population included all patients in the safety population with measurable disease at baseline per RECIST v1.1 per IRC who had ≥1 evaluable post-baseline tumor assessment unless discontinued due to disease progression or death within 7 weeks after the first dose. This population was used in the sensitivity analysis of the primary endpoint of ORR by the IRC.

be alive, and patients who remained alive were censored at the date of last adequate radiologic assessment or date of the first treatment dose if they had no baseline tumor assessment. Safety data were analyzed using descriptive statistics. All calculations and analyses were conducted using SAS version 9.4. This trial is registered on ClinicalTrials.gov (NCT03419897) and ChinaDrugTrials.org.cn (CTR20171257). Full statistical methods are provided in the online supplementary methods.

Role of the Funding Source

The funder had a role in study design, data collection, data analysis, and data interpretation. The authors had full access to the study data and had final responsibility for the decision to submit for publication.

Results

Patients and Treatment

Between April 9, 2018, and February 27, 2019, 249 of 375 patients who were screened were enrolled and treated with ≥1 dose of tislelizumab (Fig. 1). The most common inclusion criteria which patients failed at screening were adequate organ function and having received ≥1 prior line of systemic therapy for advanced HCC. Patient characteristics and demographics are shown in Table 1. Of the enrolled patients, 137 (55%) had received 1 prior line of systemic therapy, 102 (41%) had received 2 prior lines of systemic therapies, and 9 (4%) had received ≥3 prior lines of systemic therapies. One patient who received sorafenib as adjuvant therapy had overt progression/recurrence of disease after sorafenib treatment, with BCLC stage C disease at study entry, and was therefore included in the 1 prior-line group for all analyses. One patient who received apatinib as first-line and sorafenib as second-line therapy was included in the ≥2 prior-lines group. Most patients (n = 235; 94%) had received prior treatment with sorafenib and/or lenvatinib (online suppl. Table S2). Most commonly used prior systemic therapies also included regorafenib (n = 49; 20%), pyrimidine analogs (n = 46; 19%), and platinum compounds (n = 40; 16%). Other chemotherapy agents or protein kinases were reported in a small number of patients (both in less than 5% of patients). Determination of PD-L1 status was not required at baseline and was established for 158 (64%) patients.

At the time of data cutoff (June 30, 2021), median follow-up duration was 12.7 months (range 0.1–37.0) and nine of the 249 patients were still receiving study treatment. The median duration of tislelizumab treatment was 4.1 months (range 0.5–36.6). The most common reason for treatment discontinuation was PD in 184 (74%) patients (Fig. 1). Most patients (n = 155; 62%) were treated with subsequent systemic anticancer therapies after tislelizumab treatment discontinuation (the majority were treated with protein kinase inhibitors [n = 111] or chemotherapy [n = 30]). The median number of subsequent systemic therapy regimens was 1.0 (range 1.0–4.0). Regorafenib (n = 40; 16%) was the most frequently given subsequent systemic therapy (online suppl. Table S3).

Table 1. Patient demographics and baseline characteristics

Characteristic	All patients (N = 249)
Median age (range), years	62 (28–90)
Male	217 (87)
Race	
Asian	126 (51)
Black or African American	4 (2)
White	96 (39)
Other	2 (1)
Unknown	21 (8)
Region	
Mainland China/Taiwan	122 (49)
Europe	127 (51)
ECOG PS	
0	129 (52)
1	120 (48)
BCLC staging at study entry	
B	24 (10)
C	225 (90)
Child-Pugh A[a]	248 (100)
Extrahepatic spread	200 (80)
Location of metastases	
Lungs	113 (45)
Lymph nodes	90 (36)
Bone	40 (16)
Peritoneum	29 (12)
Adrenal gland	27 (11)
Other	22 (9)
Soft tissue	10 (4)
Muscle	5 (2)
Macrovascular invasion	46 (19)
PD-L1 status	
Positive (TC ≥1%)	15 (6)
Negative (TC 0%)	143 (57)
Unknown	91 (37)
Baseline AFP	
>400	112 (45)
≤400 μg/L	136 (55)
Unknown	1 (0)
HCC etiology	
Hepatitis B[b]	128 (51)
Hepatitis C	36 (15)
History of alcohol abuse	77 (31)
NASH	42 (17)
Prior liver local regional therapy	200 (80)
Prior anticancer surgery in anatomical areas other than the liver	42 (17)
Median duration of study follow-up (range), months	12.7 (0.1–37.0)

Data presented as n (%) unless otherwise indicated. BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PD-L1, programmed death-ligand 1; TC, tumor cells. [a] One patient had Child-Pugh classification B (score of 7) at study entry. [b] Five patients had HBV/HCV dual infection (n = 1, 1 prior line; n = 4, ≥2 prior lines).

Efficacy

Across the study population, confirmed ORR was 13% (n = 32; 95% CI: 9–18; one-sided p value based on the historical response rate of 7% was 0.0001). ORR was consistent for patients who received 1 prior line of therapy (13%; n = 18; 95% CI: 8–20) and ≥2 prior lines of therapy (13%; n = 14; 95% CI: 7–20). Five (2%) patients had CR, 27 (11%) patients had PR, 100 (40%) patients had SD, and 107 (43%) patients had PD as their best overall response. Ten (4%) patients were not assessable as they did not have a post-baseline assessment or the post-baseline assessment was unevaluable (Table 2). There was 97% concordance between investigator-assessed (online suppl. Table S4) and IRC-assessed (Table 2) tumor responses.

At data cutoff, eight (25%) of the 32 responses were ongoing, and the median DoR was not reached after a median follow-up of 27.4 months (range 25.0–28.4). The first response was mostly identified at the first or second tumor assessment (week 6 and week 12, respectively) (Fig. 2), and the median time to response was 2.8 months (range 1.2–10.2 months). Of the responding patients, 66% (95% CI: 46–80) were event-free at 24 months.

The CBR was 23% (n = 56; 95% CI: 17–28), and the DCR was 53% (n = 132; 95% CI: 47–59). Median PFS was 2.7 months (95% CI: 1.4–2.8) (online suppl. Fig. S2). Median PFS was 2.6 months (95% CI: 1.4–2.8) and 2.7 months (95% CI: 1.4–2.8) for patients who received 1 prior line of therapy and ≥2 prior lines of therapy, respectively. The estimated PFS rates at 6, 12, and 24 months were 25% (95% CI: 20–31), 16% (95% CI: 12–22), and 10% (95% CI: 6–15), respectively.

At data cutoff, the median OS was 13.2 months (95% CI: 10.8–15.2) (Fig. 3). The 6-, 12-, and 24-month OS rates were 76% (95% CI: 71–81), 53% (95% CI: 46–59), and 32% (95% CI: 26–38), respectively. Median OS was 13.8 months (95% CI: 10.5–19.1) and 12.4 months (95% CI: 9.9–15.2) for patients who received 1 prior line of therapy and ≥2 prior lines of therapy, respectively. Investigator-assessed secondary endpoints were consistent with the corresponding IRC-assessed endpoints (online suppl. Tables S4, S5). In an additional exploratory analysis, the median OS for patients who continued tislelizumab treatment beyond investigator-assessed disease progression (n = 204) was 14.1 months (95% CI: 11.8–19.1), and the median OS for the group of patients who discontinued tislelizumab at the time of investigator-assessed disease progression was 10.7 months (95% CI: 7.5–13.5).

ORR was generally similar across prespecified subgroups of patients, including region, HCC etiology, macrovascular invasion, and PD-L1 expression status (online suppl. Fig. S3). Reductions from baseline in target lesion tumor burden were observed in 90 (38%) of all treated patients by IRC assessment (online suppl. Fig. S4).

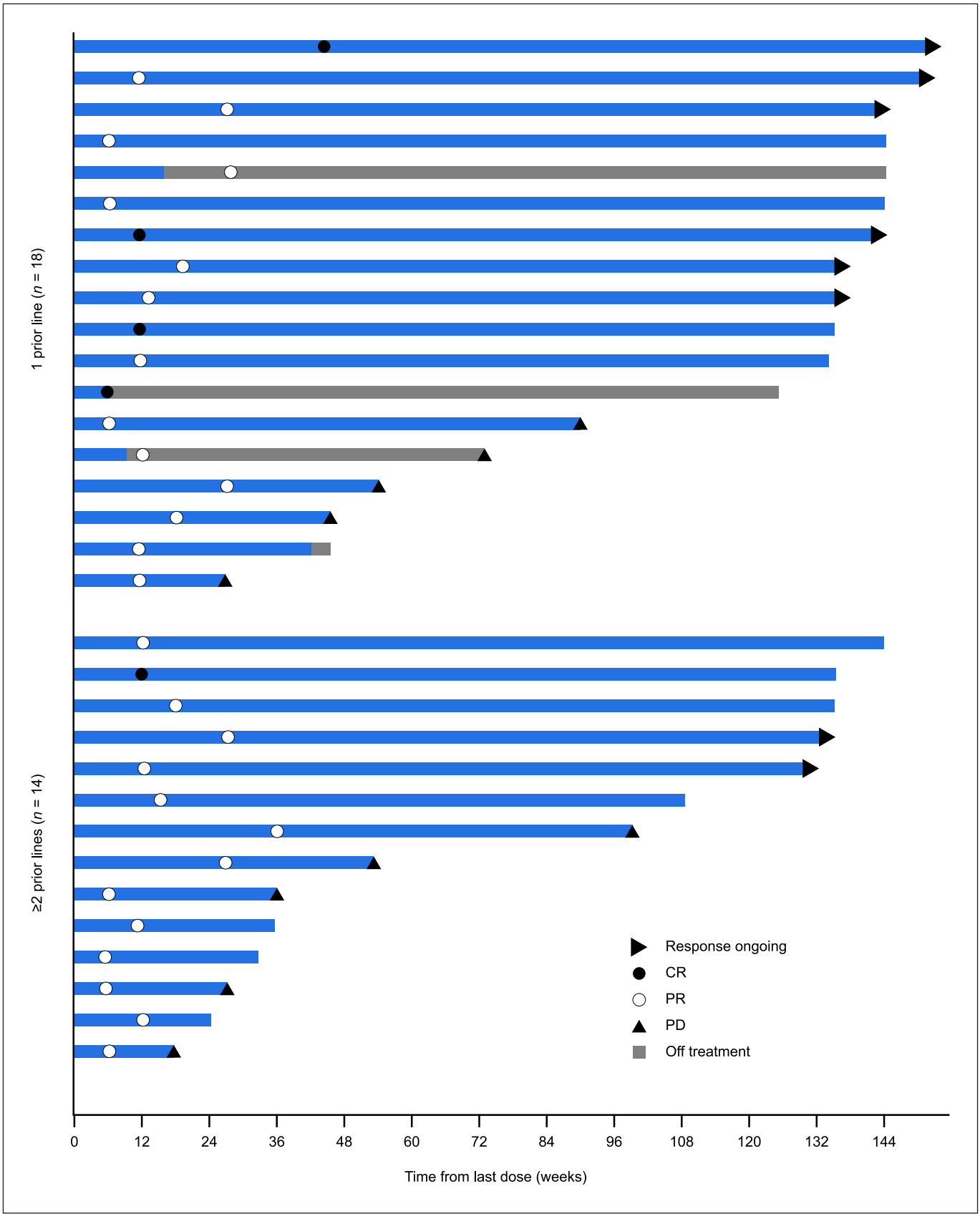
Table 2. Summary of antitumor activity by the IRC

	All patients (N = 249)	1 prior line[a] (n = 138)	≥2 prior lines (n = 111)
ORR (CR + PR), % (95% CI)	13 (9–18)	13 (8–20)	13 (7–20)
CR, n (%)	5 (2)	4 (3)	1 (1)
PR, n (%)	27 (11)	14 (10)	13 (12)
SD[a], n (%)	100 (40)	55[a](40)	45 (41)
PD, n (%)	107 (43)	60 (44)	47 (42)
Not assessable[b], n (%)	10 (4)	5 (4)	5 (5)
CBR (CR + PR + SD ≥24 weeks), % (95% CI)	23 (17–28)	26 (19–34)	20 (14–26)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; IRC, Independent Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. [a] Including 2 patients assessed as non-CR/non-PD due to lack of measurable disease per IRC. [b] No post-baseline assessment or an unevaluable post-baseline assessment.

Fig. 2. Time to response and DoR by the IRC. Each bar represents an individual patient who responded to tislelizumab (N = 32). Treatment period is plotted only up to the time of the last tumor assessment for patients who were still on treatment. Patients without ongoing response or PD either discontinued the study or were censored with an initiation of new anticancer therapy. CR, complete response; DoR, duration of response; IRC, Independent Review Committee; PD, progressive disease; PR, partial response.

(For figure see next page.)


1 prior line (n = 18)
≥2 prior lines (n = 14)
Response ongoing
CR
PR
PD
Off treatment
0
12
24
36
48
60
72
84
96
108
120
132
144
Time from last dose (weeks)

2

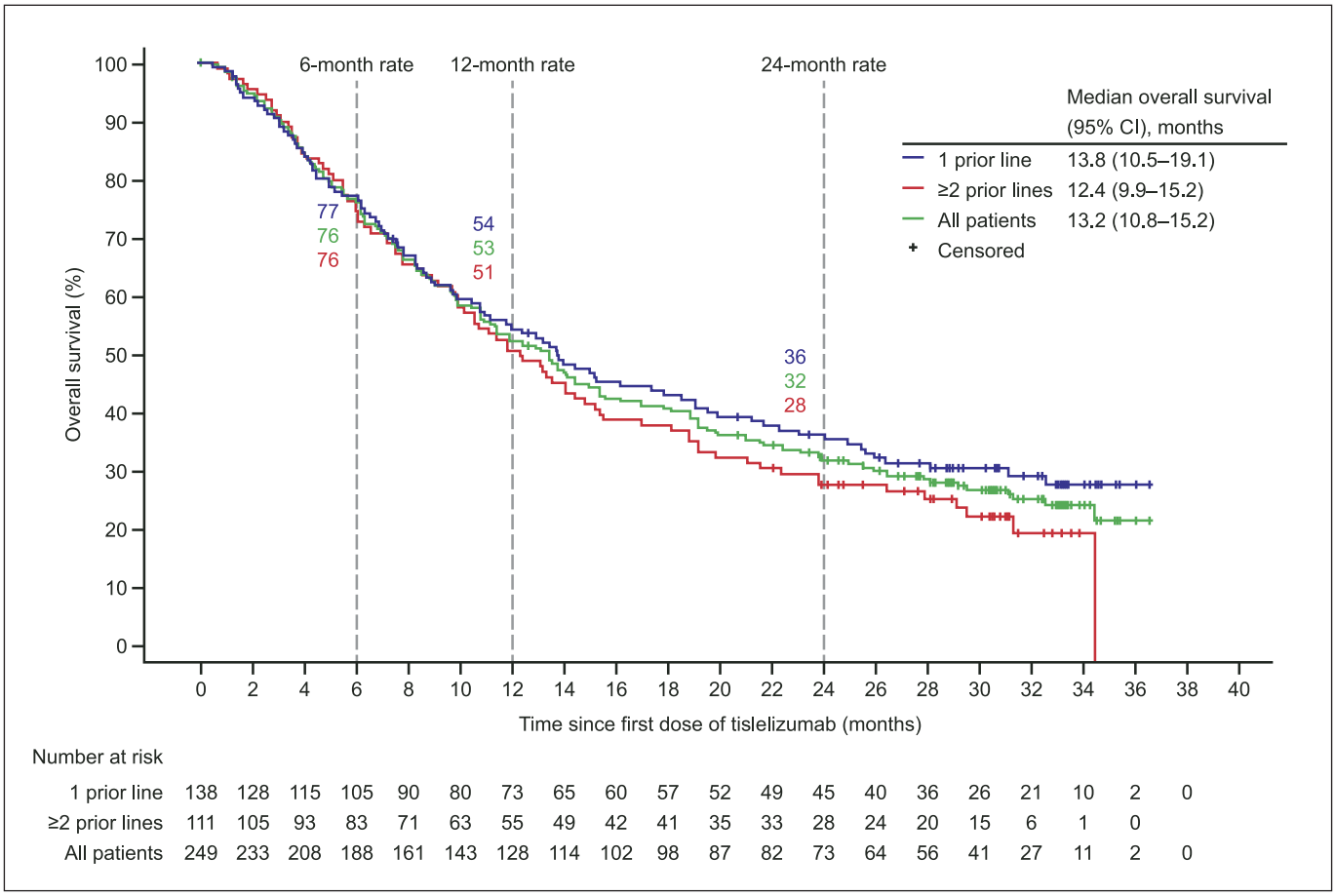


Fig. 3. Kaplan-Meier curve for OS. CI, confidence interval; OS, overall survival.

Safety and Tolerability

Most patients (n = 236; 95%) reported ≥1 treatment-emergent AE (TEAE). Serious TEAEs were reported in 93 (37%) patients (Table 3). Grade ≥3 TEAEs were reported in 123 (49%) patients; the most common were increased aspartate aminotransferase (AST; n = 19; 8%), ascites (n = 16; 6%), and increased blood bilirubin (n = 13; 5%). Overall, 79 (32%) patients had dose delays attributed to TEAEs; the most frequent were increased AST (n = 12; 5%) and increased alanine aminotransferase (ALT) (n = 10; 4%).

Overall, 158 (64%) patients reported ≥1 treatment-related AE (TRAE). At least one serious TRAE was reported in 18 (7%) patients. The most common TRAEs occurring in ≥5% of patients are reported in Table 4. Thirteen (5%) patients discontinued study treatment due to a TRAE. Grade ≥3 TRAEs were reported in 38 (15%) patients; the most common were increased AST (n = 7; 3%) and increased ALT (n = 3 [1%]). A total of 46 (19%) patients had dose delays attributed to TRAEs; the most frequent were increased AST (n = 8; 3%) and increased ALT (n = 7 [3%]). There was a similar incidence of TRAEs among patients who received 1 prior line of therapy and those who received ≥2 prior lines of therapy (Table 4).

Fifty-five (22%) patients experienced ≥1 immune-mediated AE, based on sponsor assessment; the most common were hypothyroidism (n = 17; 7%), skin reactions (n = 16; 6%), hepatitis (n = 10; 4%), and hyperthyroidism (n = 6; 2%) (Table 4). Overall, 22 of the 55 patients who experienced ≥1 immune-mediated AE received concomitant systemic corticosteroids. Eleven (4%) patients experienced grade ≥3 immune-mediated events. Nine (4%) patients experienced serious immune-mediated events, and five (2%) experienced serious immune-mediated events that led to discontinuation. Ten patients were categorized as having developed immune-mediated hepatitis (Table 4), defined by the clustered term of the preferred terms: increased AST, increased ALT, hepatitis,

Table 3. Summary of AEs

	All patients (*N* = 249)	1 prior line (*n* = 138)	≥2 prior lines (*n* = 111)
TEAEs			
Any grade	236 (95)	130 (94)	106 (96)
Grade ≥3	123 (49)	69 (50)	54 (49)
SAEs	93 (37)	53 (38)	40 (36)
Led to discontinuation	28 (11)	18 (13)	10 (9)
Led to death	26 (10)[a]	16 (12)	10 (9)
Led to dose modification[b]	79 (32)	45 (33)	34 (31)
TRAEs			
Any grade	158 (64)	91 (66)	67 (60)
Grade ≥3	38 (15)	24 (17)	14 (13)
SAEs	18 (7)	13 (9)	5 (5)
Led to discontinuation	13 (5)	10 (7)	3 (3)
Led to death	0 (0)	0 (0)	0 (0)
Led to dose modification[b]	46 (19)	27 (20)	19 (17)

Data presented as *n* (%). AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event. [a] Twenty three patients had disease progression reported as the primary cause of death. [b] Dose delay; dose reduction was not permitted.

Table 4. Frequency of AE

	All patients (*N* = 249)		1 prior line (*n* = 138)		≥2 prior lines (*n* = 111)	
	any grade	grade ≥3	any grade	grade ≥3	any grade	grade ≥3
TRAEs						
Increased AST	32 (13)	7 (3)	18 (13)	5 (4)	14 (13)	2 (2)
Increased ALT	23 (9)	3 (1)	13 (9)	2 (1)	10 (9)	1 (1)
Hypothyroidism	21 (8)	0 (0)	10 (7)	0 (0)	11 (10)	0 (0)
Pruritus	20 (8)	0 (0)	11 (8)	0 (0)	9 (8)	0 (0)
Asthenia	19 (8)	0 (0)	9 (7)	0 (0)	10 (9)	0 (0)
Increased blood bilirubin	17 (7)	2 (1)	12 (9)	1 (1)	5 (5)	1 (1)
Pyrexia	15 (6)	0 (0)	7 (5)	0 (0)	8 (7)	0 (0)
Rash	15 (6)	0 (0)	8 (6)	0 (0)	7 (6)	0 (0)
Diarrhea	14 (6)	1 (0)	6 (4)	1 (1)	8 (7)	0 (0)
Fatigue	13 (5)	2 (1)	7 (5)	1 (1)	6 (5)	1 (1)
Increased blood creatine phosphokinase MB	13 (5)	0 (0)	7 (5)	0 (0)	6 (5)	0 (0)
Immune-mediated AEs						
≥1 event	55 (22)	11 (4)	28 (20)	7 (5)	27 (24)	4 (4)
Hypothyroidism	17 (7)	0 (0)	8 (6)	0 (0)	9 (8)	0 (0)
Skin reaction	16 (6)	1 (0)	7 (5)	0 (0)	9 (8)	1 (1)
Immune-mediated hepatitis[a]	10 (4)	6 (2)	5 (4)	4 (3)	5 (5)	2 (2)
Increased AST	4 (2)	2 (1)	3 (2)	2 (1)	1 (1)	0 (0)
Increased ALT	3 (1)	1 (0)	2 (1)	1 (1)	1 (1)	0 (0)
Hepatitis[b]	3 (1)	2 (1)	1 (1)	1 (1)	2 (2)	1 (1)
Hyperthyroidism	6 (2)	0 (0)	3 (2)	0 (0)	3 (3)	0 (0)

Data presented as *n* (%). Immune-mediated AEs were based on sponsor assessment. TRAEs occurring in ≥5% of patients (any grade). Immune-mediated AEs occurring in ≥3 patients. Data are listed in order of decreasing frequency. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MB, myocardial band; TRAE, treatment-related adverse event. [a] Clustered term (includes the following preferred terms: increased AST, increased ALT, hepatitis, immune-mediated hepatitis, and increased transaminases). [b] Preferred term.

immune-mediated hepatitis, and increased transaminases. The incidence of pneumonitis (n = 2, [1%]) and colitis (n = 1, [0.4%]) was low.

Overall, 180 (72%) deaths were reported as of data cutoff. Twenty-six (10%) patients experienced a TEAE leading to death; however, none of these deaths were considered related to the treatment by the investigators, and the primary cause of death was PD for all but 3 of the 26 patients (ascites and hepatic encephalopathy [n = 1], infectious pneumonia [n = 1], and upper gastrointestinal hemorrhage [n = 1]).

Hepatitis B viral load increases from screening were observed in seven (5%) out of 128 patients with a medical history of HBV infection. All 7 patients were surface antigen positive at study entry and had been receiving antiviral treatment. All events were nonserious and did not result in discontinuation of tislelizumab treatment. HBV DNA decreases were observed after change of antiviral treatment in 3 patients. No patients had hepatitis C reactivation.

Discussion

In this open-label, multiregional, phase 2 trial, tislelizumab monotherapy demonstrated durable clinical activity in patients with advanced HCC who had received ≥1 prior systemic therapy, excluding immune checkpoint inhibitors. The study population was well represented geographically, with an almost equal number of patients from Asia and Europe. Furthermore, almost half of the study population were heavily treated (patients who had received ≥2 prior lines of therapy), representing a population with a high unmet medical need, not readily represented in prior HCC trials.

Tislelizumab demonstrated evident clinical activity in this study, with an IRC-assessed ORR of 13%. Patients' first responses were mostly identified at the first or second tumor assessment, and the median time to response was 2.8 months (range 1.2–10.2), suggesting that tislelizumab achieved rapid responses. Similar objective responses were observed in other studies that investigated PD-1/PD-L1 inhibitors in patients with advanced HCC who had progressed on or were unable to tolerate first-line sorafenib therapy, including pembrolizumab in KEYNOTE-224 (17%) [30], KEYNOTE-240 (18%) [31], and KEYNOTE-394 (14%) [14], and nivolumab in CheckMate-040 (15–20%) [32]. A key difference of the RATIONALE-208 study from the aforementioned studies is the substantial proportion (n = 111/249; 45%) of patients who had received ≥2 prior lines of therapy. Furthermore, objective responses in RATIONALE-208 were consistent with the CheckMate-459 study (15%), which investigated first-line nivolumab in patients with advanced HCC [33].

Tislelizumab demonstrated robust clinical activity in patients with advanced HCC. A substantial number of objective responses were consistently observed across prespecified subgroups, regardless of number of prior treatment lines, region, prior therapies received, HCC etiology (including NASH), PD-L1 expression level, and other key demographic and disease characteristics, such as macrovascular invasion, extrahepatic spread, BCLC staging, and AFP >400 μg/L [34]. Notably, in some studies, patients with nonalcoholic fatty liver disease/NASH-driven HCC treated with PD-1/PD-L1 inhibitors in real-world settings have poorer clinical outcomes compared to patients with other etiologies [35, 36]. However, tislelizumab demonstrated encouraging clinical activity in patients with NASH, although this subpopulation comprised a small portion of the overall study population (42 [17%] patients) and some of these patients had multiple HCC etiologies (online suppl. Fig. S3).

After a median follow-up of ≥2 years (27.4 months), the median DoR was not reached (range 14.6 months – not estimable) at the time of data cutoff, and the estimated 24-month event-free rate was 66%. Importantly, the results demonstrated the durable antitumor activity of tislelizumab in patients with previously treated HCC. These data suggest that the median DoR observed with tislelizumab compares favorably to other PD-1/PD-L1 inhibitors, e.g., pembrolizumab in KEYNOTE-224 (not reached [range 3.1–14.6 + months]) [30], KEYNOTE-240 (13.8 months) [31], and nivolumab in CheckMate-040 (17 months) [32] in patients with advanced HCC in the second-line setting or beyond.

Tislelizumab showed survival benefit (median OS of 13.2 months) in a heavily pretreated patient population. OS was comparable with other PD-1/PD-L1 inhibitors in similar trials, e.g., pembrolizumab in KEYNOTE-224 (median OS of 12.9 months) [30] and KEYNOTE-240 (median OS of 13.2 months) [31]. The durable responses and median OS observed with tislelizumab bolster the clinical treatment choice of PD-1 inhibitors in patients with advanced HCC. The number of prior lines of therapy did not considerably impact response or survival estimates, indicating a potential role for tislelizumab as second- or third-line treatment in patients with advanced HCC. Notably, the DCR was 53%, which could have positively impacted OS.

Tislelizumab monotherapy was generally well tolerated; AEs were consistent with the overall safety profile of tislelizumab observed in previous studies [26, 27] and of other PD-1/L1 inhibitors [30, 32] and were generally grade 1 and 2. Fewer than half (n = 22/55) of the patients who experienced an immune-mediated AE were prescribed concurrent corticosteroids during the course of tislelizumab treatment. The most common immune-mediated AEs, hypothyroidism, skin reaction, and hepatitis, were reported at low frequencies (7%, 6%, and 4%, respectively), and few led to treatment discontinuation. Immune-mediated AEs were similar to those observed with other PD-1/PD-L1 inhibitors [30, 32].

Viral hepatitis infection is a major cause of HCC [37]. Tislelizumab was well tolerated in the subgroup of patients with viral hepatitis. A few patients experienced HBV DNA increases, which were clinically manageable with new antiviral treatment and did not lead to discontinuation of tislelizumab treatment during the study. Hepatitis C reactivation was not observed. Notably, although in a small subgroup, one of five patients with HBV/hepatitis C virus dual infection had a confirmed objective response per the IRC. These data indicate clinical activity of tislelizumab in a patient with HBV/hepatitis C virus dual infection, a population excluded from and not evaluated in other studies [30, 32]. Data from a larger patient population from a randomized, controlled study are required to determine if tislelizumab could be a potential treatment option in this patient population.

A limitation of the study is the absence of a randomized, controlled study design. A large, multiregional, randomized, phase 3 study comparing tislelizumab with sorafenib as a first-line treatment in adult patients with advanced HCC (NCT03412773) is currently ongoing. The open-label nature of the RATIONALE-208 study may have affected the evaluation of efficacy and safety by the investigator. However, the blinded review of response data by the IRC provided unbiased efficacy evaluations in support of the primary endpoint. Patients with Child-Pugh A liver function were enrolled to mitigate any potential confounding effect from impaired liver function on efficacy outcomes.

This multiregional, single-arm, phase 2 study demonstrated tislelizumab had encouraging and durable clinical activity in patients with advanced HCC who had received ≥1 prior systemic therapy. The safety profile was similar to that of tislelizumab in other indications. Durable clinical activity was consistently observed with tislelizumab regardless of the number of prior treatment lines, PD-L1 expression status, HCC etiology, and geographic region, supporting potential multiregional use of tislelizumab as a second- or third-line treatment option for patients with advanced HCC, who represent a patient population with a high unmet need.

Acknowledgments

The authors would like to thank the participants of the study, the study investigators, all the study staff, and the clinical and statistical support teams for their contributions to the study. Medical writing support, under the direction of the authors, was provided by Kirsty Millar, MSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

Statement of Ethics

All relevant Institutional Review Boards/Independent Ethics Committees on human research reviewed the protocol and amendments and approved the study, which was carried out in accordance with the International Conference on Harmonization Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations. This study protocol was reviewed and approved by the National Taiwan University Hospital Research Ethics Committee, approval number 201801128MSB. All participants provided written informed consent prior to enrollment. Trial registration: ClinicalTrials.gov, NCT03419897.

Conflict of Interest Statement

Zhenggang Ren reports consulting support from AstraZeneca, F. Hoffmann-La Roche Ltd., and Merck. Michel Ducreux reports research support to the institution from F. Hoffmann-La Roche, Ltd., Merck, Keocyt, and Bayer and receives consulting support from AMGEN, F. Hoffmann-La Roche Ltd., Ipsen, Merck, MSD, Bayer, BeiGene, Ltd., Hutchinson, AstraZeneca, Eli Lilly, Keocyt, and Celgene. Ghassan K. Abou-Alfa reports research support to the institution from Arcus, Agios, AstraZeneca, Bayer, BioNTech, BMS, Celgene, Flatiron, Genentech/Ltd./F. Hoffmann-La Roche Ltd., Genoscience, Incyte, Polaris, Puma, QED, Sillajen, and Yiviva and receives consulting support from Agios, Alnylam, AstraZeneca, Autem, Bayer, BeiGene, Ltd., Berry Genomics, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech Ltd./F. Hoffmann-La Roche Ltd., Genoscience, Helio, Incyte, Ipsen, Legend Biotech, Merck, MINA, QED, Redhill, Sillajen, Surface Oncology, Therabionics, Twoxar, Vector, and Yiviva. Philippe Merle reports grants from Ipsen and Genosciences and receives advisory board fees from F. Hoffmann-La Roche Ltd., BMS, AstraZeneca, Bayer, Eisai, MSD, Ipsen, Lilly, and Genosciences. Weijia Fang, Zhiwei Li, Julien Edeline, Lihua Wu, Sheng Hu, Tao Zhang, Jean-Frédéric Blanc, Hongming Pan, Chia-Jui Yen, Albert Tran, Guoliang Shao, Mohamed Bouattour, Yajin Chen, Jinlin Hou, Yuxian Bai, Ming-Mo Hou, and Zhiqiang Meng declare no competing interests. Eric Assenat reports research support to the institution from F. Hoffmann-La Roche Ltd. and Bayer and receives consulting support from AMGEN, F. Hoff-

mann-La Roche Ltd., Ipsen, Bayer, AstraZeneca, and Boston. Lorenza Rimassa reports receiving consulting support from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, F. Hoffmann-La Roche Ltd., Sanofi, Servier, Taiho Oncology, and Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, F. Hoffmann-La Roche Ltd., and Sanofi; travel expenses from AstraZeneca; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Ltd., Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, F. Hoffmann-La Roche Ltd., and Zymeworks. Paul Ross reports grants from Bayer and Sanofi. Tim Meyer is supported by the NIHR ULCH Biomedical Research Centre. David Tougeron reports receiving consulting support from Amgen, AstraZeneca, Bayer, BMS, Ipsen, MSD, Sanofi, Servier, and Merck Serono and institutional research funding from AstraZeneca, MSD, F. Hoffmann-La Roche Ltd., and Ipsen. John Wu reports employment with BeiGene, Ltd. Vincent Li reports employment and stocks with BeiGene, Ltd. Sandra Chica-Duque reports employment with BeiGene, Ltd., and her immediate family member reports a relationship with Turning Point Therapeutics. Ann-Lii Cheng reports and receives consulting support from Bristol Myers Squibb, Bayer, Eisai, Ono Pharmaceutical, AstraZeneca, Genentech Ltd./F. Hoffmann-La Roche Ltd., MSD, BeiGene, Ltd., Exelixis Ltd., Ipsen Innovation, and F. Hoffmann-La Roche Ltd.

Funding Sources

The study was sponsored by BeiGene, Ltd.

Author Contributions

Zhenggang Ren, Michel Ducreux, Ghassan K. Abou-Alfa, Ann-Lii Cheng, John Wu, Vincent Li, and Sandra Chica-Duque designed the study. Zhenggang Ren, Michel Ducreux, Ghassan K. Abou-Alfa, and Ann-Lii Cheng were steering committee members and, as such, supervised the conduct of the trial. Zhenggang Ren, Michel Ducreux, Philippe Merle, Weijia Fang, Julien Edeline, Zhiwei Li, Lihua Wu, Eric Assenat, Sheng Hu, Lorenza Rimassa, Tao Zhang, Jean-Frédéric Blanc, Hongming Pan, Paul Ross, Chia-Jui Yen, Albert Tran, Guoliang Shao, Mohamed Bouattour, Yajin Chen, Tim Meyer, Jinlin Hou, David Tougeron, Yuxian Bai, Ming-Mo Hou, and Zhiqiang Meng contributed to substantial data acquisition. John Wu was responsible for the statistical analysis and writing of the statistical analysis plan. All the authors contributed to the data analysis and interpretation. John Wu and Vincent Li have verified the underlying data. All the authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication. All the authors have contributed to, seen, and approved the final draft.

Data Availability Statement

On request, and subject to certain criteria, conditions, and exceptions, BeiGene, Ltd., will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com.

References

1 Global Burden of Disease Liver Cancer Collaboration; Abera S, Artaman A, Alam N, Alvis-Guzman N, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol. 2017 Dec 1;3(12):1683–91.

2 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 Feb 4;71(3):209–49.

3 Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology. 2010 Apr;51(4):1274–83.

4 Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review. Bethesda, MD: National Cancer Institute; 1975–2017. p. 2020.

5 Xie DY, Ren ZG, Zhou J, Fan J, Gao Q. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. Hepatobiliary Surg Nutr. 2020 Aug;9(4):452–63.

6 Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, et al. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (2019 Edition). Liver Cancer. 2020 Dec;9(6):682–720.

7 Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv238–55.

8 Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO Guideline. J Clin Oncol. 2020 Dec 20;38(36):4317–45.

9 Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. Cancer Cell. 2015 Sep 14;28(3):285–95.

10 Federico P, Petrillo A, Giordano P, Bosso D, Fabbrocini A, Ottaviano M, et al. Immune checkpoint inhibitors in hepatocellular carcinoma: current status and novel perspectives. Cancers. 2020 Oct 18;12(10):3025.

11 Li H, Qin S, Liu Y, Chen Z, Ren Z, Xiong J, et al. Camrelizumab combined with FOLFOX4 regimen as first-line therapy for advanced hepatocellular carcinomas: a sub-cohort of a multicenter phase Ib/II study. Drug Des Devel Ther. 2021;15:1873–82.

12 Wong JSL, Kwok GGW, Tang V, Li BCW, Leung R, Chiu J, et al. Ipilimumab and nivolumab/pembrolizumab in advanced hepatocellular carcinoma refractory to prior immune checkpoint inhibitors. J Immunother Cancer. 2021 Feb;9(2):e001945.

13 US Food and Drug Safety Administration. Combined FDA and Merck Sharp & Dohme, BLA 125514/S-024 KEYTRUDA (pembrolizumab), briefing document for the April 29, 2021 meeting of the Oncologic Drugs Advisory Committee (Hepatocellular carcinoma). 2021. Available from: https://www.fda.gov/media/147858/download (accessed January 4, 2022).
14 Qin S, Chen Z, Fang W, Ren Z, Xu R, Ryoo B-Y, et al. Pembrolizumab plus best supportive care versus placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): phase 3 KEYNOTE-394 study. J Clin Oncol. 2022:40(4_suppl):383.
15 Rimassa L, Danesi R, Pressiani T, Merle P. Management of adverse events associated with tyrosine kinase inhibitors: improving outcomes for patients with hepatocellular carcinoma. Cancer Treat Rev. 2019 Jul;77:20–8.
16 European Medicines Agency. Cabozantinib (Cabometyx). Summary of product characteristics. 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/cabometyx (accessed January 4, 2022).
17 US Food and Drug Safety Administration. Prescribing information. In. Exelixis Inc. Cabozantinib (Cabometyx); 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208692s010lbl.pdf (accessed January 4, 2022).
18 Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018 Jul 5;379(1):54–63.
19 Zhang T, Song X, Xu L, Ma J, Zhang Y, Gong W, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother. 2018 Jul;67(7):1079–90.
20 Wang J, Lu S, Yu X, Hu Y, Sun Y, Wang Z, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non–small-cell lung cancer: a phase 3 randomized clinical trial. JAMA Oncol. 2021;7(5):709–17.
21 Sandhu S, Hill A, Gan H, Friedlander M, Voskoboynik M, Barlow P, et al. Tislelizumab, an anti-PD-1 antibody, in patients with urothelial carcinoma (UC): results from an ongoing phase I/II study. Ann Oncol. 2018;29:x28.
22 Shen L, Kato K, Kim S-B, Ajani JA, Zhao K, He Z, et al. Rationale 302: randomized, phase 3 study of tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma. J Clin Oncol. 2021;39(15_suppl):4012.
23 Yang Y, Pan J, Wang H, Qu S, Chen N, Chen X, et al. 121O rationale 309: a randomized, global, double-blind, phase III trial of tislelizumab (TIS) vs placebo, plus gemcitabine + cisplatin (GP), as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC). Ann Oncol. 2021;32:S1430.
24 Li J, Xu Y, Zhang A, Gao Y, Gao Q, Zhang Y, et al. A phase 2 study of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable or metastatic microsatellite instability-high/mismatch repair deficient solid tumors. J Clin Oncol. 2021;39(15_suppl):2569.
25 Song Y, Gao Q, Zhang H, Fan L, Zhou J, Zou D, et al. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. Leukemia. 2020 Feb;34(2):533–42.
26 Wang S, Huang X, Bai Y-X, Yuan Y, Li J, Wang Z, et al. Preliminary results with tislelizumab, an investigational anti-PD-1 antibody, in Chinese patients with nasopharyngeal cancer (NPC). J Clin Oncol. 2019;37(15_suppl):2556.
27 Desai J, Deva S, Lee JS, Lin CC, Yen CJ, Chao Y, et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. J Immunother Cancer. 2020 Jun;8(1):e000453.
28 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228–47.
29 Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56–66.
30 Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018 Jul;19(7):940–52.
31 Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, Phase III Trial. J Clin Oncol. 2020 Jan 20;38(3):193–202.
32 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, noncomparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun 24;389(10088):2492–502.
33 Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022 Jan;23(1):77–90.
34 Hiotis SP, Rahbari NN, Villanueva GA, Klegar E, Luan W, Wang Q, et al. Hepatitis B vs. hepatitis C infection on viral hepatitis-associated hepatocellular carcinoma. BMC Gastroenterol. 2012;12(1):64.
35 Kudo M. Impaired response to immunotherapy in non-alcoholic steatohepatitis-related hepatocellular carcinoma? Liver Cancer. 2021 Jul;10(4):289–95.
36 Pfister D, Núñez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature. 2021;592(7854):450–6.
37 Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021 Jan 21;7(1):6.